Pediatric Heart Transplantation: Transitioning to Adult Care (TRANSIT): Feasibility of a Pilot Randomized Controlled Trial

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ABSTRACT

Background: Young-adult heart transplant recipients transferring to adult care are at risk for poor health outcomes. We conducted a pilot randomized controlled trial to determine the feasibility of and to test a transition intervention for young adults who underwent heart transplantation as children and then transferred to adult care.

Methods: Participants were randomized to the transition intervention (4 months long, focused on heart-transplant knowledge, self-care, self-advocacy, and social support) or usual care. Self-report questionnaires and medical records data were collected at baseline and 3 and 6 months after the initial adult clinic visit. Longitudinal analyses comparing outcomes over time were performed using generalized estimating equations and linear mixed models.

Results: Transfer to adult care was successful and feasible (ie, excellent participation rates). The average patient standard deviation of mean tacrolimus levels was similar over time in both study arms and < 2.5, indicating adequate adherence. There were no between-group or within-group differences in percentage of tacrolimus bioassays within target range ($> 50\%$). Average overall adherence to treatment was similarly good in both groups. Rates of appointment keeping through 6 months after transfer declined over time in both groups.

Conclusions: The feasibility of the study was demonstrated. Our transition intervention did not improve outcomes. (*J Cardiac Fail 2019;25:948–958*)

Keywords: Heart transplantation, Transition program.

Introduction

The transition from childhood to adulthood, referred to as emerging adulthood (ie, the interval between 18 and 25 years of age)[1] is generally characterized by instability, vulnerability, poor judgment and decision making, risk-taking behaviors, and emotional reactivity.[2] This major life transition can be related to poor health outcomes for chronically ill young adults, especially those who have undergone solid-organ transplantation.[3–6] In a retrospective cohort study of primary heart transplant (HT) recipients < 40 years of age, graft-failure rates were highest among 17- to 29-year-olds.[5] Poor adherence to the health care regimen, especially with transfer from pediatric to adult health care, is related to poor health outcomes in young adult recipients of transplants.[7–13] Other factors related to outcomes during transfer from pediatric to adult care include cognitive capacity (eg, cognitive delay and deficits), psychological factors (eg, emotional maturity, anxiety, distress, feelings of abandonment by the pediatric health care team, and uncertainty about the new team), social factors (eg, parental fears, negotiating the changing role of parental support),

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demographic factors (eg, age and gender), as well as inadequate planning by clinicians, and systems issues (eg, poor communication and coordination between clinical teams as well as insurance issues).[14–16] Interrupted use of health care services during and after transfer of care has been reported frequently.[9,17,18]

The goal of transition, defined as "a complex set of beliefs, skills and processes that facilitate the movement from pediatric care to adult-centered care,"[9,19] is to provide comprehensive, developmentally appropriate health care in a coordinated, uninterrupted and seamless manner across centers in partnership with patients.[20] In contradistinction, transfer of care is simply the movement to a new health care setting[20] and, for our trial, indicated the establishment of care in the adult HT program. The National Survey of Children with Special Health Care Needs found that 60% of youth did not receive the services necessary to transition successfully from pediatric to adult care facilities.[21] Findings from a more recent national survey were more bleak, with only 17% and 14% of youth with and without special health care needs, respectively, receiving transition-planning support.[22]

Furthermore, the literature on transition interventions to facilitate transfer of young adults with chronic illnesses to adult care is poor or nonexistent, and young adults are not well-equipped to receive care in adult health care systems.[2,8,23–27] A recent Cochrane Review evaluated the effectiveness of transition interventions designed to improve transfer of care from pediatric to adult health services.[28] Endpoints included disease-specific outcomes, readiness to transfer, treatment adherence, disease knowledge, health-related quality of life, and resource utilization. The authors reported that no firm conclusions could be drawn regarding the effectiveness of interventions and that other models of transitional care need to be evaluated.[28] Weissberg-Benchell et al[29] reviewed 3 interventions to facilitate transfer of care, including transition programs, and also concluded that additional research was needed, including incorporating intervention work not only in the pediatric setting but also in the adult care setting and assessing post-transfer health-related outcomes and clinic attendance at adult clinics beyond the first visit.

A Consensus Conference Report from Bell et al[8] identified critical milestones to achieve and components of successful transfer for young adult patients after solid organ transplantation prior to transfer of care. Milestones included understanding of the cause of organ failure, implications of the transplant on health, demonstrating responsibility for one's own health care, and readiness to move into adulthood. Components of successful transfer included assessment of readiness to transfer; development and implementation of an individualized transition plan of care (including the pediatric and adult teams and patient and family, supporting the concept of shared accountability); facilitation of primary and preventive health care; implementation of strategies to enhance medication adherence (eg, education on medications, self-care strategies and more frequent clinic visits early after transfer of care); and promotion of educational and vocational planning. Development of educational tools, such as printed materials or videos for self-learning, were recommended. Finally, Bell and colleagues[8] identified critical research questions regarding the transfer to adult care by young adult recipients of solid organs, including: "Can a formal transition program improve medical and psychosocial outcomes (eg, rates of acute rejection, disease knowledge and treatment adherence)?"

In response to these critical questions, we developed and conducted a pilot randomized controlled trial, Pediatric Heart Transplantation: Transitioning to Adult Care (TRANSIT). We tested a transition intervention (ie, a standardized, tailored transition program focused on increasing HT knowledge, self-care and self-advocacy skills and enhancing social support) designed to improve outcomes (ie, adherence to immunosuppression and the medical regimen, adverse events and resource use) for emerging adults who underwent HT as children and transferred to adult care (ClinicalTrials.gov=NCT02090257).

Methods

Aims and Hypotheses

Our primary aim was to assess the feasibility of TRANSIT. We hypothesized that $\geq$ 84% of patients with HTs would be retained, $\geq$ 80% would fully participate in the transition program, and $\geq$ 80% of questionnaires would be completed at all time periods.

Our secondary aim was to determine the efficacy of the intervention (ie, the transition program) in the following outcomes: (1) within-participant standard deviation (SD) of average tacrolimus blood levels at specific time points (primary endpoint); (2) tacrolimus levels within target range (determined by HT cardiologists); (3) self-report of adherence to the medical regimen; (4) episodes of adverse events (including acute rejection); and (5) use of health care resources. We hypothesized that through 3 and 6 months after transfer to adult care, patients in the intervention arm would have (1) lower tacrolimus variability (ie, SD $<$ 2.5)[30–32]; (2) $>$ 50% of tacrolimus levels within target range; (3) better self-reported adherence to the medical regimen; (4) fewer episodes of treated acute rejection; (5) higher rates of clinic attendance and calcineurin inhibitor (CNI) blood-draw appointments; and (6) fewer all-cause days of rehospitalization than patients who received usual care.

Design and Theoretical Framework

We used a prospective, multisite, nonblinded, variable block size, 1-to-1 randomized controlled trial design. Emerging adult ($>$ 18 years) recipients of HT were randomized to either the transition program, conducted by pediatric and adult HT coordinators, or to usual care. HT coordinators in each trial arm had no contact with patients in the other arm. Components of our transition program and outcomes were evaluated at baseline (the final pediatric clinic

visit) and at 3 and 6 months after the initial adult clinic visit. Although we recognize that discussions of transferring care often begin much earlier than late adolescence and emerging adulthood,[8] we selected the final pediatric clinic visit for study enrollment because that was the time at which actual transfer of care was planned.

The Pai and Drotar[33] Treatment Adherence Impact model guided assessment of outcomes in our transition program (Online Supplement 1). Adherence was assessed for 2 levels of outcome of the Treatment Adherence Impact model: (1) patient level, the most proximal to patients and considered to be the most sensitive indicator; and (2) mesolevel, the more distal, including health care resource utilization. Patient-level outcomes were tacrolimus levels, adverse events and self-report of adherence to the medical regimen; mesolevel outcomes were rates of keeping appointments and of rehospitalization.

Sample, Setting and Randomization

This trial received Institutional Review Board approval at all participating institutions, and participants provided written informed consent. Study inclusion criteria, previously described, were > 18 years of age; post HT at participating children's hospitals and ready to transfer care (as determined by the pediatric transplant cardiologist as per usual practice at each institution); able to speak, read and write English; and physically able to participate.[34] Young adults with developmental delays were excluded because they have the potential for additional and unique transition planning outside the scope of the intervention for this study, including a focus on level of functioning and guardianship.[8,35] We also excluded young adults who had had psychiatric hospitalizations within the previous 3 months, based on recommendations by a coinvestigator and child psychologist on our team and supported by literature recommending that young adults with acute mental health issues transfer during a time of stability vs crisis so as to reduce the additional stress of meeting and becoming comfortable with a new health care team while undergoing intense psychiatric treatment.[36] Thus, our plan was to enroll young adults without these additional challenges.

Between March 1, 2014, and August 31, 2016, we screened 143 young adults post-HT and enrolled 88 (62%) of them at 6 U.S. pediatric HT programs (Figure 1). Of the 55 patients not enrolled, 16 did not meet inclusion criteria, 6 declined to participate, and 33 did not participate for other reasons, including transfer to nonpartner institutions (n = 15), concern about health status (n = 8), transfer delay due to use of multiple other pediatric services (n = 5), developmental delay (n = 2), insurance not accepted at the adult partner institution (n = 1), concerns about adherence to the medical regimen (n = 1), and psychiatric hospitalization within the previous 3 months (n = 1).

Variable block (sizes 2 or 4) 1:1 randomization was used to allocate patients to a study arm within each clinical site (n = 43 [intervention] and n = 45 [usual care]). Participants transferred to the partner adult HT program for follow-up care. Most programs had a freestanding children's hospital that was partnered with a separate adult hospital on the same medical school campus. For 1 program, the partner program was contiguous to the pediatric program. At the end of participation in the study, 37 patients were retained in the intervention arm and 41 in the usual care arm (Figure 1).

Data Collection

Data were collected from medical records and self-report questionnaires. Medical records and use of resource data included diagnosis of HF, medical/surgical/psychosocial history, immunosuppression and CNI levels, and adverse events as well as treatments, clinic visits, visits for CNI level blood draws, and rehospitalizations. Three CNI levels prior to transfer of care were included, and up to 3 CNI levels through 3 months post-transfer (1-, 2- and 3-month blood draws) and up to 5 CNI levels through 6 months post transfer (1-, 2-, 3-, 4-, and 6-month blood draws) were included. Questionnaires assessed components of the intervention (ie, HT Knowledge Questionnaire,[37,38] Transition Readiness Assessment Questionnaire[39] and Social Support Index[40]) and of the patient (Assessment of Problems with the HT Regimen[41]) and patient-level outcomes (Table 1). Psychometric support of the questionnaires has been reported previously.[34] Patients were given a $30 gift card after completion of each set of questionnaires.

Intervention

The intervention (ie, the transition program) was approximately 4 months in duration and had 2 phases (Online Supplement 2). During phase 1, at the pediatric site, patients were instructed to complete 4 education modules that were focused on HT knowledge, self-care, self-advocacy, and support (Online Supplement 3). The modules were provided on a flash drive as a power point presentation with voice-over, and a written self-test was completed within 2 weeks of receipt of the materials, followed by a discussion with the pediatric HT coordinator. The HT education modules and self-test were developed by investigators from existing HT education materials[37,38] and were reviewed by a patient-education expert for content clarity, format and reading level (determined to be at the fifth grade level).[42,43] Patients were asked to complete modules at home; expected time to complete modules and the self-test was 2 hours. If patients did not have access to a computer at home, other ways to access a computer were discussed (eg, using a computer at the local library). After completion of the modules and self-test, patients were asked to schedule an appointment with the pediatric HT coordinator to discuss completion of these materials face-to-face (preferred) or by telephone. If the patient did not contact the pediatric HT

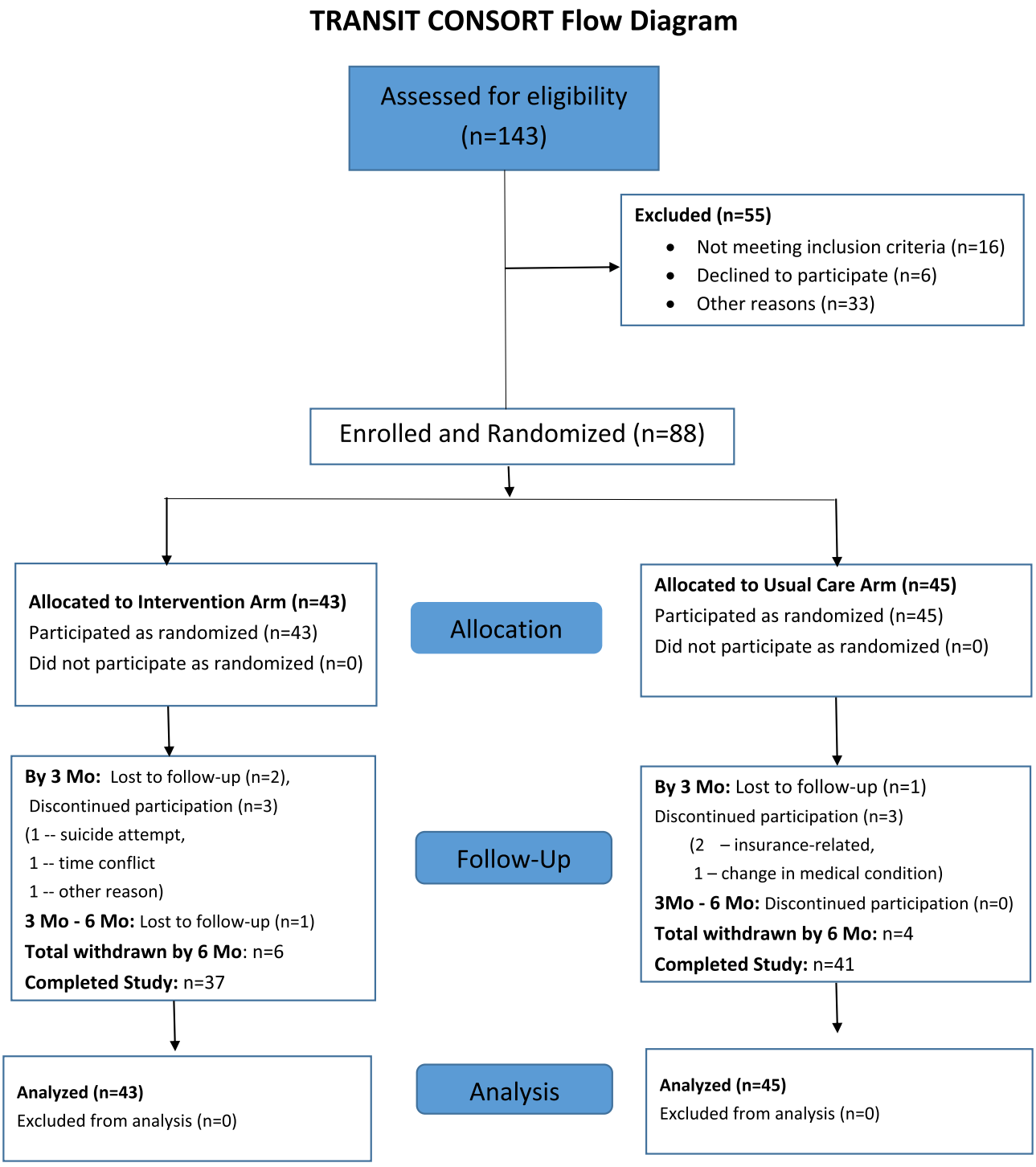

Fig. 1. TRANSIT consort flow diagram. This figure demonstrates flow of patients through the study.

coordinator by 2 weeks after receipt of the modules, the pediatric HT coordinator telephoned the patient to follow-up and schedule the review of materials. At least 3 phone calls were made, per protocol. Patients were also asked to schedule a first adult HT clinic appointment in 4 weeks.

The discussions of the modules and the self-test scores (including missed self-test items) were shared by the pediatric HT coordinator with the adult HT coordinator prior to the first adult HT clinic appointment in order to hand-off baseline educational strengths and deficits. Phase 2 (Online Supplement 4) began at transfer to adult care and included assessment, reinforcement and the tailoring of the education module's content at the first clinic visit by the adult HT coordinator. Tailoring of discussions focused on areas in which the patient had deficits. Three phone calls were made by the adult HT coordinator at 6, 8 and 10 weeks after the first visit to further assess and tailor discussions. The intervention concluded at a 3-month clinic visit that included

Table 1. Measures of components of the intervention and outcomes reflecting treatment adherence

Area assessed	Data Source	Response Range	Description
Components of the intervention			
Knowledge of heart transplant	HT Knowledge Questionnaire[37,38]	0−100 Higher score = more correct responses	20-item tool; questions measure knowledge of medications (eg, purpose of taking tacrolimus), follow-up care (eg, how to schedule and prepare for the first adult clinic visit), lifestyle (eg, identifying components of a healthy lifestyle), health status and benefits/risks of HT (eg, identifying symptoms, benefits and medical risks), and transition to adult care (eg, identifying components of a successful transition to adult care)
Readiness to transition to adult care	Transition Readiness Assessment Questionnaire (TRAQ)[39]	*2−6 Higher score = higher readiness to transfer: 2 = no, I don't know how; 3 = no, I don't know how but I want to learn; 4 = no, but I am learning to do this; 5 = yes, I have started doing this; and 6 = yes, I always do this when I need to	29-item survey measuring readiness to transition from pediatric to adult health care, with 2 domains: skills for self-care (eg, filling prescriptions and scheduling clinic follow-up) and skills for self-advocacy (eg, reporting symptoms to the health care team and making a list of questions prior to a clinic visit)
Social support	Social Support Index (SSI)[40]	1−4 1 = very dissatisfied 4 = very satisfied	Questionnaire measuring satisfaction with support: emotional, tangible and overall support for 15 illness-related tasks (eg, personal care and taking medications)
Outcomes reflecting treatment adherence			
Patient level			
Adherence to medical regimen	Assessment of problems with the HT regimen[41]	1−4 1 = hardly ever 4 = all of the time	15-item questionnaire measuring adherence to 15 aspects of the HT medical regimen (ie, medications [eg, immunosuppressants], lifestyle [eg, diet and exercise], appointment keeping [eg, clinic attendance], and health monitoring [eg, monitoring symptoms])
Bioassays for tacrolimus and cyclosporine	Medical records		Bioassays, target range and within-target range (yes/no and individualized for patients per HT cardiologists)
Adverse events	Medical records		Episodes of adverse events, including specifically acute rejection
Mesolevel			
Health care utilization	Medical records		Clinic and CNI bioassay appointment attendance rates and all-cause days rehospitalized
Other data			
Demographic questionnaire	Demographic data form		Items included age, gender, race, ethnicity, marital status, children, education level, living arrangements, work, and health insurance for patients

CNI = calcineurin inhibitor; HT = heart transplant.
*If patients indicated 1 = not needed for my care; those responses were not included in analyses of that item.

final assessment and discussion of the adequacy of self-care, self-advocacy and support, including reinforcement of HT knowledge, as needed.

Usual Care

The usual care group received a standard transfer of care (Online Supplement 2). Patients met with the pediatric HT coordinator to discuss processes, concerns and questions regarding transferring care and were asked to schedule a first adult HT clinic appointment in 4 weeks. At the first adult clinic visit, the adult HT coordinator provided standard adult program information. Patients were contacted via telephone by the adult transplant usual care nurse 6, 8 and 10 weeks later to inquire about concerns after transferring care. Final discussions about transferring care were held at the 3-month clinic visit.

Treatment Fidelity

HT coordinators at sites were trained via webinar to implement the scripted key messaging for clinic visits and telephone calls. Treatment fidelity was monitored at all sites via assessment of audio recordings of pediatric and adult HT coordinator discussions for selected patients in each study arm, followed by review of the recordings by 1 of the principal investigators (PIs) or lead study coordinator with provision of feedback.[44] Approximately 10% of HT coordinators (including both pediatric and adult) were monitored at each site. Additional monitoring was planned, per protocol,

if sites performed poorly based on assessment of audio recordings. HT coordinators followed the scripted messaging very well, and minimal directed feedback was necessary. No additional monitoring was conducted.

Statistical Analyses

Variables were summarized using the mean and SD or the median accompanied by first and third quartiles, if continuous, or counts/percentages, if categorical. Comparisons between the intervention and usual care arms were based on 2-sample *t* tests with unequal variances and the Satterthwaite approximation for the number of degrees of freedom, for continuous variables. Group comparisons of categorical variables were based on the χ^2 or Fisher exact test (if cell count < 5). To compare percentages of within-target measurements between the 2 study arms, we used generalized estimating equations, given that potentially multiple assessments per patient were available at each time point. Longitudinal analyses comparing outcomes over time were performed using linear mixed models with an intercept random effect, a center random effect and group, time and group interaction, with time as fixed effects. An unstructured correlation matrix was employed to account for repeated measures recorded within each individual over time. In each model, we adjusted for the number of years since primary HT. Model coefficients for study arm and time are referred to as group and time effect, respectively. Analyses were performed in SAS v. 9.4 (SAS Institute, Cary, NC), and significance was declared at a 2-sided 5% level, with no multiplicity adjustments.

Results

Demographic and Clinical Characteristics

Baseline demographics, clinical characteristics, and psychosocial history (collected from medical records according to notes by mental health professionals) did not differ significantly between groups (Table 2). The average age in both groups was 21 years, and the majority were males, white, educated, single, and living with parents. HF etiology, predominantly cardiomyopathy and congenital heart disease, and time since primary transplant were similar in both groups. Patients in both groups, on average, took longer than expected (4 weeks) to transfer care to the adult HT program (intervention group = 80 days; usual care group = 64 days).

Feasibility

Rates of retention through 6 months post-transition were higher than the hypothesized 84%. Overall, the rate was 78 of 88 (89%); in the intervention arm, 37 of 43 (86%); and in the usual care arm, 41 of 45 (91%). Rates of participation in the intervention arm were also higher than the hypothesized 80%: phase 1 (pediatric site = 90%, with self-reported length of time to complete modules and self-tests = 71.5 + 34.9 minutes and 26.4 + 19.6 minutes, respectively) and phase 2 (adult site: first adult clinic visit = 95%, telephone follow-up [week 6 = 100%, week 8 = 93%, week 10 = 97%, and 3-month clinic visit = 100%). Last, rates of questionnaire completion were higher than the hypothesized 80%: baseline (intervention arm = 43/43 [100%] and usual care arm = 45/45 [100%]); 3 months (intervention arm = 37/38 [97%] and usual care arm = 36/41 [88%]), and 6 months (intervention arm = 30/37 [81%] and usual care arm = 36/41 [88%]).

Components of the Adherence-Enhancing Intervention

Significant differences were not detected across time within groups or between groups regarding overall HT-related knowledge (73% to 75% item-level correct responses in both groups); satisfaction with support, which was very high in both groups (3.7-3.9 in both groups, range: 1 = very dissatisfied to 4 = very satisfied); and self-advocacy skills (4.4-4.5 in both groups, range: 2 = no, I don't know how, to 6 = yes, I always do this when I need to) (Online Supplement 5, A–C). Self-advocacy scores between 4 and 5 indicate that patients are learning how to or are starting to use these skills. Self-care skills increased significantly over time in the usual care group but not in the intervention group (4.1 to 4.4, $P = 0.007$ and 4.2 to 4.4, P = NS, respectively) (Online Supplement 5, D). HT-related knowledge subscale scores were also similar for both groups, with highest scores for lifestyle (item-level range: intervention = 73.6%–75.6% and usual care = 75.0%–77.8%) and medications (item-level range: intervention = 72.4%–77.6%, and usual care = 71.1%–73.9%), and lowest scores for follow-up care (item-level range: intervention = 69.0%–72.9% and usual care = 67.1%–73.3%) and health status (item-level range: intervention = 65.5%–68.2% and usual care = 61.1%–67.4%). Small nonsignificant increases were detected over time for satisfaction with support subscales: tangible support (intervention = 3.8–4.0, and usual care = 3.8–3.9) and emotional support (intervention = 3.8–3.9 and usual care = 3.7–3.9).

Outcomes

Patient Level. Immunosuppression. The majority of patients were taking tacrolimus (n = 29 intervention and n = 26 usual care). At baseline, the 3 most recent tacrolimus levels were included in the analyses, which included 100% of patients in both study arms. For SD estimation, only patients with 2 or more tacrolimus level values were included in analyses through 3 months (69% of patients in the intervention arm and 73% of patients in the usual care arm) and through 6 months (97% intervention arm, 100% usual care arm) post-transfer. Mean tacrolimus levels did not differ significantly by time and by group/time interaction (intervention 6.5–6, usual care 5.6–6 [baseline to 6 months]) (On-line Supplement 6, A). The average within-patient SD of tacrolimus levels was similar over time and was < 2.5 in both study arms, indicating adequacy of adherence (intervention 1.6–1.5, usual care 1.3–1.4 [baseline to 6 months]) (Online Supplement 6, B). There were no significant between-group or within-group differences in percent of tacrolimus levels within target range over time (intervention 69%–75%, usual care 72%–58% [baseline to

Table 2. Baseline demographic characteristics, clinical and psychosocial history, resource utilization, and transition time by study arm

Demographic characteristics	Intervention N = 43		Usual care N = 45		*P* value
Age (mean + SD)	21.3 ± 3.2		21.5 ± 3.3		0.75
Female gender (n/%)	19	(44%)	22	(49%)	0.66
Caucasian race (n/%)	35	(81%)	34	(76%)	0.51
Education (n/%)					0.75
Some high school (9−12)	4	(9%)	6	(13%)	
High school graduate	13	(30%)	8	(18%)	
> High school education	26	(60%)	31	(68%)	
Current marital status (n/%)					0.10
Married	1	(2%)	2	(4%)	
Partner	4	(9%)	0	(0%)	
Single	38	(88%)	43	(96%)	
Working for income (n/%)	17	(40%)	26	(58%)	0.09
Living alone (n/%)		0.96			
Yes	2	(5%)	2	(4%)	
No	41	(95%)	43	(96%)	
If no, living with parents	35	(85%)	37	(86%)	0.93
Clinical and psychosocial history					
Heart failure diagnosis (n/%)					0.28
Cardiomyopathy	21	(48.8%)	20	(44.4%)	
Congenital heart disease	20	(46.5%)	25	(55.6%)	
Myocarditis	2	(4.7%)	0	(0)	
Medical history: comorbidities (n/%)					
Hypertension (requiring medical therapy)	19	(44%)	18	(40%)	0.69
Cardiac allograft vasculopathy	10	(23%)	12	(27%)	0.71
Chronic kidney disease	8	(19%)	15	(33%)	0.12
Neoplasm (not PTLD)	8	(19%)	8	(18%)	0.92
Arrhythmia requiring pacemaker, ICD, CRT	5	(12%)	2	(4%)	0.21
Hyperlipidemia (requiring medical therapy)	5	(12%)	9	(20%)	0.28
Surgical history:					
Years since primary heart transplant (mean + SD)	43	13.5 ± 7.6	45	14.8 ± 6.6	0.41
Heart retransplant (n/%)	10	(23%)	5	(11%)	0.13
Immunosuppression (n/%)					
tacrolimus (Prograf and Hecoria)	30	(70%)	28	(62%)	0.46
cyclosporine	9	(21%)	10	(22%)	0.88
mycophenolate (Cellcept and Myfortic)	26	(60%)	23	(51%)	0.38
azathioprine	3	(7%)	5	(11%)	0.50
sirolimus	20	(47%)	22	(49%)	0.82
Episodes of acute rejection (within 6 months prior to final pediatric clinic visit) (n/%)					0.23
0	39	(91%)	43	(96%)	
1	4	(9%)	1	(2%)	
2	0	(0)	1	(2%)	
Episodes of major infection (within 6 months prior to final pediatric clinic visit) (n/%)					0.56
.0	39	(91%)	43	(96%)	
.1	3	(7%)	1	(2%)	
.2	1	(2%)	1	(2%)	
Psychosocial history (n/%)					
Behavioral issues (eg, poor adherence, substance abuse)	4	(9%)	4	(9%)	0.95
Mental disorders (eg, anxiety, depression)	10	(23%)	8	(18%)	0.52
Social support (limited)	7	(16%)	6	(13%)	0.70
Resource utilization (events within 6 months prior to final pediatric clinic visit) (n/%)					
Rehospitali-zations	11	(26%)	7	(16%)	0.24
Missed clinic visits	8	(19%)	4	(9%)	0.18
Missed CNI blood draws	6	(14%)	11	(24%)	0.21
Length of time to transition					
Duration (days) (mean ± SD)	41	79.9 ± 59.9	45	63.9 ± 41.3	0.16
Duration (days) (median [Q1, Q3])	41	58 (41, 101)	45	49 (35, 81)	0.28

CNI = calcineurin inhibitor; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter defibrillator; PTLD = post-transplant lymphoproliferative disease; SD = standard deviation.

6 months]) (Online Supplement 6, C). Notably, the frequency of levels within target range was higher in the intervention group than in the usual care group at 3 months (intervention 83%, usual care 51%) and 6 months.

Self-reported Adherence. Average overall self-reported adherence to the treatment regimen (1 = hardly ever to 4 = all of the time) was similarly good in both groups, and no significant group/time interactions were detected. Significant

improvement across time was detected for the usual care group but not for the intervention group, (3.5−3.7, $P = 0.003$, and 3.6−3.7, $P =$ NS, respectively) (Online Supplement 7, A). In both groups, average self-reported adherence subscale scores were highest for medications (range 3.7−3.9) and appointment-keeping (range 3.6−3.8) and lowest for lifestyle (range 2.8−3.1) and health monitoring (range 2.6−3.1) (Online Supplement 7, B−E). No significant differences in time or group/time interaction were found for subscale scores, except for medication differences over time for the usual care but not the intervention group (3.7−3.9, $P = 0.045$ and 3.8−3.9, $P =$ NS, respectively) (Online Supplement 7, B−E).

Adverse events. The number of patients with adverse events through 3 and 6 months was low to moderate, with a trend toward more adverse events in the intervention group by 6 months. (Table 3). The average number of events per patient through 3 and 6 months was similar in the 2 trial arms (Table 3). The number of episodes of treated acute rejection were low through 3 and 6 months but differed significantly between groups through 6 months (intervention = 5, usual care = 0, $P = 0.021$) (Table 3), with 3 of the 5 episodes observed in a single patient.

Mesolevel. Appointment keeping and rehospitalization. Rates of keeping clinic and CNI blood-draw appointments were similar in both groups through 3 months and 6 months but declined over time (Table 3). The all-cause number of rehospitalizations was low and was similar in both groups through 3 and 6 months after transfer (Table 3). The number of days of rehospitalization was also similar in the 2 groups through 3 and 6 months after transfer, with the majority of rehospitalizations occurring in fewer than 10 days.

Discussion

To our knowledge, this is the first pilot trial to test, directly and methodically, a transition intervention designed to improve outcomes for young-adult recipients of HT who are transferring to adult care. We concluded that the conduct of our pilot trial was feasible, with excellent rates of retention and participation in the intervention. However, the hypothesis for the primary endpoint of our secondary aim was not met. Both groups had similar tacrolimus SD < 2.5, indicating adequate adherence.[30−32] Additionally, there were no significant between-group differences in self-report of adherence to the medical regimen, although usual care participants had improved self-reported adherence (overall and for medications) over time. Adverse events, except episodes of acute rejection through 6 months, did not differ between groups over time. Last, there were no between-group differences in appointment keeping or rehospitalization.

Insights into Findings from our Pilot Trial

Although this was a negative pilot trial, it was informative, and from it we learned a fair amount and are able to offer insights into the hurdles surrounding transition planning for young adult recipients of HT who transfer from pediatric to adult services. This information may provide guidance for future trials and patient care. The lack of difference in tacrolimus SDs between groups over time may

Table 3. Patient-level and mesolevel outcomes between groups

	Intervention	Usual Care	*P* value
Patient-level outcomes			
Adverse events			
Patients with adverse event through 3 months (n/%)	13/38 (34%)	7/41 (17%)	0.12
Patients with adverse events through 6 months (n/%)	16/37 (43%)	9/41 (22%)	0.055
Events per patient through 3 months (mean)	0.40	0.16	0.07
Events per patient through 6 months (mean)	0.53	0.27	0.11
Episodes of treated acute rejection through 3 months (n/%)	3 (8%)	0 (0%)	0.11
Episodes of treated acute rejection through 6 months (n/%)	5 (14%)	0 (0%)	0.021
Participant death (n)	0	0	1.00
Mesolevel outcomes			
Resource utilization			
Appointment keeping			
Clinic attendance through 3 months (n/%)	36/38 (95%)	41/41 (100%)	0.23
Clinic attendance through 6 months (n/%)	33/37 (89%)	38/41 (93%)	0.70
Calcineurin inhibitor blood-draw appointment keeping through 3 months (n/%)	30/38 (79%)	36/41 (88%)	0.37
Calcineurin inhibitor blood-draw appointment keeping through 6 months (n/%)	25/37 (68%)	32/41 (78%)	0.32
Rehospitalization			
All-cause rehospitalizations through 3 months (n/%)	5 (13%)	2 (5%)	0.25
All-cause rehospitalizations through 6 months (n/%)	8 (22%)	4 (10%)	0.21
Number of days rehospitalized through 3 months (n/%)			0.80
0	35 (92%)	39 (95%)	
1−5	1 (3%)	1 (2%)	
6−10	2 (5%)	1 (2%)	
Number of days rehospitalized through 6 months (n/%)			0.17
0	32 (86%)	39 (95%)	
1−5	2 (5%)	1 (2%)	
6−10	3 (8%)	0 (0%)	
11−15	0	1 (2%)	

have been multifactorial. At baseline, patients in both groups had tacrolimus SDs < 2.5, high levels of self-reported medication adherence and modestly high HT knowledge scores regarding medication, and they reported high levels of satisfaction with their support. Thus, fairly high medication knowledge, high adherence and support in both groups at baseline may have led to a ceiling effect, dampening the potential impact of our intervention on outcomes. The relationship of knowledge and support with measures of adherence has been documented in the literature.[45–47]

Additionally, Killian[48] reported that parental factors (eg, family composition) were related to adherence after pediatric heart and lung transplantation. The majority of recipients of HT in both groups in our study were single and living with their parents. Thus, parents in both groups may have continued to manage care and not encourage self-care, which may also have contributed to a lack of difference in adherence between groups.

Motivation and clinical trial participation, as well as the Hawthorne effect, may also have influenced our negative findings. Regarding enrollment, one might question whether only young HT recipients who were "motivated" to improve outcomes joined the study. The very small increase in self-care skills in the usual care group over time may reflect enrollment by more motivated young adult recipients of HT. However, this particular finding must be interpreted cautiously because statistical significance does not always imply a clinically important difference.[49]

The Hawthorne effect also may have contributed to our negative pilot trial (ie, patients in both groups had frequent CNI bioassays [ie, frequent monitoring of medication-taking behavior] after transfer to adult care, which may have inadvertently supported good medication-taking behavior in both groups). Notably, although > 50% of patients in both groups had tacrolimus levels within target range after transfer, the rates were higher in the intervention group, suggesting that our intervention may have had some effect on adherence to taking immunosuppressant medication.

The decline in appointment-keeping over time in both study arms is consistent with that of other studies.[50–52] Our finding of low knowledge scores regarding follow-up care supports this idea. Finally, although rates of rehospitalization were low in both groups, low scores regarding knowledge of health status in both groups were similar to findings from other studies.[53] These results suggest the need for a stronger focus on health monitoring and follow-up care in future trials of transition planning.

Clinical and Research Implications

Transition planning should begin prior to transfer of care.[54] The exact timing for initiating this dialogue remains unknown; early adolescence has been recommended by some,[35] with the caveat that transfer of care should occur when patients are stable as outpatients.[36,55] Furthermore, we identified high satisfaction with support for patients transferring care in both arms of our study. Thus, family-focused interventions may also be beneficial as well as those focused on individuals. Regarding parental involvement, the literature supports gradual movement of parents from a role of coordinating care to one of supporting care, thus modeling and encouraging young-adult independence and self-responsibility.[8,29,54]

The inclusion of adult HT coordinators in our transition program is novel. Current transition programs involve transition planning by pediatric practitioners, who facilitate introduction to adult HT clinicians and services, but the transition planning concludes shortly after transfer to adult care.[29] Our transition program included discussions with not only pediatric HT coordinators, but also with adult HT coordinators, who tailored discussions to concerns and deficits that were identified after transfer to adult services. Thus, engagement of adult clinicians in transition-related care after transfer to adult services may be beneficial in improving outcomes, but this requires further study. We also recommend extending the duration of transition planning to longer than 3 months after transfer to adult care in future trials; this idea is supported by our finding that self-advocacy and self-management did not change over time for patients randomized to our intervention group. Implementation and testing of this novel synergistic approach to transition-related care requires a multidisciplinary pediatric/adult collaborative team to develop policies and protocols. Testing of the transition program and its impact on important outcomes, at both the patient level and mesolevels, later as well as early after transfer of care, are of critical importance.

Study Limitations

Our pilot trial was limited by a small sample size and short duration of follow-up after transfer of care. Also, the majority of our cohort was fairly homogeneous (ie, single, white, > than a high school education, and living with parents), thus reducing sample diversity and potentially biasing our findings (ie, patients being less at risk for poor adherence during transfer of care) and limiting generalizability. Additionally, readiness to transfer care to a partner adult HT program was subjective because it was determined by pediatric transplant cardiologists. This may have introduced bias because only the most capable patients were selected. All of our participating pediatric sites have a legacy of excellence as HT centers, and transition efforts at participating pediatric centers may have begun several months or years before actual transfer of care (at which time patients enrolled in our study), which may have impacted our findings. None of our participating centers had formal transition programs in place.

There were also potential limitations in the intervention. The education modules were completed at home without direct supervision. On-site supervision of module completion may have ensured that the full dose of the intervention was received and may have increased the potential for finding significant differences in outcomes between groups.

Participant-reported length of time to module completion and self-testing were, on average, almost as long as expected. Furthermore, although our curriculum addressed important HT and general medical knowledge and skills, content not included in our curriculum may be relevant. Other teaching modalities (eg, videos or classroom learning followed by discussion) may also have been more appealing, thus enhancing completion of educational materials.

Conclusions

The feasibility of our study was achieved through excellent retention and participation in the intervention. However, our transition intervention did not improve the outcomes selected. Notably, proof of feasibility is an important first step that provides a platform for development of future interventions in larger randomized controlled trials.

Based on what we have learned from this informative pilot trial, we recommend that future trials of transition planning for young adult recipients of HT begin earlier than the time when patients are scheduled to transfer care and that they last longer after actual transfer to adult services. We believe that our transition content addressing knowledge, self-care, self-advocacy and support may promote good patient- and mesolevel outcomes. However, this content needs to be tested in a larger, more diverse young-adult patient population. Furthermore, we recommend including content in the intervention that is directed toward facilitating change in the parental role. Use of teaching modalities that are more in tune with the way young adults learn today may enhance completion of all materials.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.06.011.

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